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Increasing Bacterial Resistance in Pediatric Acute Conjunctivitis (1997–1998)

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We sought to determine the current level of resistance in *Haemophilus influenzae* and *Streptococcus pneumoniae*, the primary pathogens of pediatric conjunctivitis. Between January 1997 and March 1998, we prospectively cultured acute conjunctivitis in 250 ambulatory pediatric patients from rural Kentucky whose average age was 24.3 months. In those 250 cases, 106 *H. influenzae* (42% of the total) and 75 *S. pneumoniae* (30% of the total) pathogens were isolated, with no growth or no pathogen resulting in 79 cases (32% of the total). Beta-lactamase was detected in 60 (69%) of 87 tested strains of *H. influenzae*. Among 65 isolates of *S. pneumoniae* tested for penicillin susceptibility, 44 (68%) were susceptible, 17 (26%) were resistant, and 4 (6%) were intermediate. Conjunctivitis with acute otitis media was observed in 97 patients (39%), and *H. influenzae* was recovered in 57% of these 97 cases. As for in vitro activity, ciprofloxacin, ofloxacin, and tetracycline were the most active; and gentamicin, tobramycin, polymyxin B-trimethoprim, and polymyxin B-neomycin were intermediately active. Sulfamethoxazole possessed no activity against either pathogen. Beta-lactamase production was detected in 69% of *H. influenzae* strains, which still remains the primary causative pathogen of both conjunctivitis and conjunctivitis-otitis syndrome. Penicillin-nonsusceptible *S. pneumoniae* was observed in 32% of 65 patients with *S. pneumoniae* conjunctivitis, with most strains being penicillin resistant.

Acute conjunctivitis is the most common ocular infection in childhood, usually affecting children younger than 6 years old with a peak incidence between 12 and 36 months (3). Pediatric acute conjunctivitis is diagnosed by clinical signs of ocular purulent discharge or hyperemia of bulbar conjunctiva. The etiology of this infection has been documented as bacterial in 54 to 73% of pediatric cases (3, 20). The pathogens predominantly recovered include nontypeable *Haemophilus influenzae* (44 to 68% of cases) and *Streptococcus pneumoniae* (7 to 21% of cases). Concomitant infection with acute otitis media (AOM) has been coined the conjunctivitis-otitis syndrome by Bodor (4) and is associated with *H. influenzae* in 20 to 73% of cases and with *S. pneumoniae* in 12 to 20% of cases (4, 10). Other rare bacterial pathogens of conjunctivitis include *Moraxella catarrhalis*, *Streptococcus mitis*, and *Streptococcus pyogenes* (10, 22).

Clinicians nearly always empirically treat acute conjunctivitis with topical antimicrobial therapy. The disease is mild, cultures are rarely obtained because of expense, and culture results are reported days later (13). Compared with placebo, topical therapy with polymyxin-bacitracin ointment has been shown to reduce by half the duration of symptoms and to achieve a 2.5-fold increase in rate of bacteriologic eradication at days 8 to 10 (31 versus 79%, respectively) (6). Furthermore, selecting among the multitude of available topical antimicrobials to treat conjunctivitis has been based on either sparse in vitro data or on earlier limited clinical efficacy trials, mostly from the 1970s and 1980s. In addition, only a single national surveillance study from multiple sites of infection in both children and adults during the 1990s has described the frequency of penicillin-nonsusceptible *S. pneumoniae* (PNSP) in conjunctivitis, but only among *S. pneumoniae* isolates (5).

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We recently reported substantial changes in antimicrobial resistance among the two most commonly isolated pathogens of AOM (1), *S. pneumoniae* and *H. influenzae*, which are also the predominant pathogens of conjunctivitis (4). In pediatric patients with acute conjunctivitis, we attempted to document the current incidence of PNSP, proportion of beta-lactamase-producing strains among isolates of *H. influenzae*, and susceptibility patterns of these particular organisms to the commonly used topical antibacterials available for treatment of conjunctivitis.

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MATERIALS AND METHODS

Patient population. During a 15-month interval between January 1997 and March 1998, as part of our routine care, we sequentially cultured a convenience sample of previously healthy patients with acute conjunctivitis at the physicians' discretion, primarily culturing those patients with obvious purulent discharge. Acute conjunctivitis was diagnosed by signs of conjunctival inflammation (bulbar conjunctival hyperemia or purulent discharge) of less than 14 days duration without signs of preseptal cellulitis. Patients were also assessed for signs of AOM and rhinorrhea. AOM was diagnosed by the presence of any one of the following tympanic membrane findings: marked hyperemia; fullness or bulging; purulent effusion or air-fluid levels; and discoloration with yellow, white (not scarred), or green opacification. Five of six general pediatricians in private practice in rural central Kentucky were previously validated otoscopists. Patient charts were also analyzed for the gender, race, and age of each patient; presence of rhinorrhea; and month of diagnosis.

Culture methods. The inferior conjunctival sac was swabbed in a single sweep for secretions or discharge with a Dacron swab, which was then streaked over chocolate and 5% sheep blood agar plates. Optochin and oxacillin disks were placed onto sheep blood agar plates, which were incubated overnight in a candle extinction jar at 35°C. Culture plates were examined the next morning. Small, mucoid CFU growing exclusively on chocolate agar, but not on sheep blood agar, were presumptively identified as *Haemophilus* strains (4). Predominant CFU growing on sheep blood agar plates, displaying characteristic morphology of pitting and alpha-hemolysis, and showing inhibition to optochin disk (zone size, >20 mm) on sheep blood agar were presumptively identified as *S. pneumoniae*. Nonsusceptibility to penicillin of these same presumptive *S. pneumoniae* colonies was assumed if the zone of inhibition around the oxacillin disk was less than 20

TABLE 1. Demographic characteristics of pathogens isolated from pediatric patients with acute conjunctivitis

Patient characteristics	Value for cultured isolate (*n*)			
	S. pneumoniae (75)	*H. influenzae* (106)	Nonpathogen or no growth (79)	Total (250)
Sex (male/female)	36 (48)[a]/39 (52)	66 (62)/40 (38)	37 (47)/42 (53)	135 (54)/115 (46)
Race (white/black)	70/5	102/4	75/4	239/11
Age (mo)				
≤2	7 (9)	15 (14)	18 (23)	37 (15)
3–24	51 (68)	68 (62)	35 (44)	148 (59)
25–48	10 (13)	14 (13)	10 (13)	33 (13)
>48	7 (9)	9 (8)	16 (20)	32 (13)

[a] Numbers in parentheses in body of table indicate percentages.

mm. All isolates were frozen and stored at −70°C and were later shipped to the research laboratory at Alcon Research, Ltd.

Confirmation and susceptibility testing. Diagnostic biochemical reactions for species confirmation were performed on viable isolates by using bioMerieux's VITEK 32 system (McDonell Douglas Health Care Systems). For *H. influenzae* and *S. pneumoniae* isolates, Neisseria/Haemophilus Identification (NHI) test cards and gram-positive identification (GPI) test cards, respectively, were used. Capsular serotyping of *H. influenzae* isolates was determined by DIFCO *H. influenzae* antiserum, and beta-lactamase production was ascertained by VITEK NHI test cards. Susceptibility testing using protocols from the National Committee for Clinical Laboratory Standards (when possible) was performed by broth microdilution on Mueller-Hinton broth with 5% lysed horse blood for *S. pneumoniae* and on Haemophilus test medium broth for *H. influenzae* (14).

Both organisms were tested for susceptibility to the following antibiotics: tobramycin, gentamicin, neomycin, polymyxin B, trimethoprim, polymyxin B-trimethoprim (1.0 μg per ml/0.8 μg per ml), polymyxin B-neomycin (1.0 μg per ml/3.2 μg per ml), ciprofloxacin, ofloxacin, tetracycline, erythromycin, chloramphenicol, and sulfamethoxazole. *S. pneumoniae* was further tested against penicillin, clindamycin, and cefazolin, and *H. influenzae* was tested against ampicillin. Penicillin susceptibility for *S. pneumoniae* was categorized as follows: susceptible, penicillin MIC of <0.1 μg/ml; intermediate penicillin resistant, penicillin MIC of 0.1 to 1.0 μg/ml; and penicillin resistant, penicillin MIC of ≥2.0 μg/ml.

Statistical analysis. Statistical analysis was performed by using the Sigmastat computer package. Chi-square for trend was used with significance set at $P < 0.05$.

RESULTS

The average age of the 250 children with acute conjunctivitis was 24.3 months, ranging from 2 weeks to 192 months (Table 1). The majority of children were younger than 24 months, 95% were white, and within each age group the rate of pathogen recovery was not significantly different. We estimated from our office charges that 830 office visits for acute conjunctivitis occurred during this interval.

H. influenzae was the pathogen most frequently recovered from cases of acute conjunctivitis, accounting for 106 isolates (42%) in 250 children. Beta-lactamase production was detected in 60 (69%) of 87 confirmed *H. influenzae* strains, and all strains were nontypeable. *S. pneumoniae* accounted for 75 (30%) isolates initially identified on blood agar plates, with 21 (28%) of 75 strains resistant by oxacillin disc testing. Penicillin susceptibility testing by broth microdilution of 65 viable strains showed that 17 (26%) were resistant, 4 (7%) were intermediately resistant, and 44 (68%) were susceptible. The penicillin MIC for three *S. pneumoniae* isolates was 8 μg/ml. Ten (4%) of 250 children had both pathogens recovered simultaneously. Nineteen and 11 isolates of *H. influenzae* and *S. pneumoniae*, respectively, initially identified were lost in the freezing and shipping process. No growth or nonpathogenic isolates were obtained in 79 (32%) of patients.

Conjunctivitis-AOM was observed in 97 (39%) of all patients. *H. influenzae*, penicillin-susceptible *S. pneumoniae*, and PNSP accounted for 57, 18, and 8%, respectively, of all cases of conjunctivitis. Within each respective group of patients, *H. influenzae* (55 [52%] of 106) was associated more frequently with AOM than either *S. pneumoniae* (24 [32%] of 75) or no growth (18 [23%] of 79) ($P < 0.01$). When patients were stratified by age 6 to 36 months (the group most likely to be affected by AOM), the rate of recovery for each pathogen in these 69 children was not significantly different than that of the overall group. Only 13% of patients were older than 48 months, and one-half of them still had a bacterial pathogen. Among the 35 infants younger than 2 months, *H. influenzae* comprised 33%, penicillin-susceptible *S. pneumoniae* comprised 11%, and PNSP comprised 3% of pathogens. No pathogen (3) and *H. influenzae* (1) were recovered in four 1-week-old infants, whereas *H. influenzae* (5), *S. pneumoniae* (2), and no pathogen (4) were recovered in 11 2-week-old infants.

Purulent discharge or erythema of the conjunctiva(e) was observed in 86 and 53%, respectively, of patients with conjunctivitis. Rhinorrhea was more commonly observed among patients whose condition had a bacterial cause (*H. influenzae* [55%] and *S. pneumoniae* [49%]), than in those without a pathogen (35%) (nonsignificant). Figure 1 shows that minimal seasonal variation was observed among patients with *S. pneumoniae* isolates, whereas *H. influenzae* was more frequently isolated between December 1997 and February 1998 ($P < 0.02$).

Tables 2 and 3 show the results of susceptibility testing for *S. pneumoniae* and *H. influenzae*, respectively. The most- to least-active antibiotics of those possessing at least minimal activity (MIC at which 90% of the isolates tested are inhibited [MIC_{90}], <32 μg/ml) against both *H. influenzae* and all levels

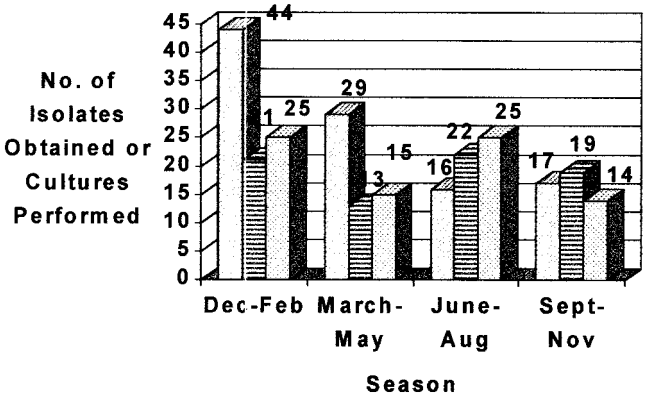

FIG. 1. Seasonal incidence of pediatric conjunctival pathogens (1997–1998) ($n = 250$ patients). The bars show *H. influenzae* (hatched), *S. pneumoniae* (striped), and no pathogen or no growth (stippled). Ten patients had both pathogens recovered: December to February (two), March to May (two), June to August (three), and September to November (three).

TABLE 2. In vitro antimicrobial susceptibilities for *S. pneumoniae* isolates obtained from pediatric patients with acute conjunctivitis (1997–1998)

Antibiotic	MIC (μg/ml)[a]					
	Penicillin-susceptible strains (n = 44)			Penicillin-nonsusceptible strains (n = 21)		
	50%	90%	Range	50%	90%	Range
Penicillin	0.02	0.06	0.004–0.06	2	8	0.5–8
Cefazolin	0.06	0.13	0.03–0.13	4	16	2–32
Tobramycin	16	32	4–64	16	64	1–64
Gentamicin	8	16	0.25–32	8	16	1–32
Neomycin	64	128	16–128	64	128	8–256
Polymyxin B[b]	>520	>520	130–520	>520	>520	260–>520
Polymyxin B–neomycin[b]	32/103	64/205	16/52–130/413	64/206	128/413	2/6.4–130/413
Trimethoprim	4	8	2–128	128	256	4–512
Polymyxin B–trimethoprim[b]	4.1/3.3	16.3/13	2/1.6–280/210	280/210	520/430	4.1/3.3–520/420
Ciprofloxacin	0.5	1	0.13–1	1	1	0.13–1
Ofloxacin	1	2	0.25–2	1	2	0.13–2
Chloramphenicol	2	4	1–4	4	16	2–16
Tetracycline	0.13	0.25	0.13–32	0.25	16	0.13–32
Erythromycin	0.13	0.13	0.03–8	4	16	0.06–16
Clindamycin	0.13	0.25	0.03–0.25	0.13	4	0.06–8
Sulfamethoxazole	32	>256	16–256	256	>256	16–>256

[a] 50% and 90%, MIC_{50} and MIC_{90}, respectively.
[b] Polymyxin B is expressed in μg/ml. The specific activity of the formualtion used was 7,500 IU/mg.

of penicillin susceptibility for *S. pneumoniae* organisms are as follows: most active, ciprofloxacin and ofloxacin; intermediately active, tetracycline, chloramphenicol, erythromycin, gentamicin, and tobramycin. The majority of strains of penicillin-susceptible *S. pneumoniae* and PNSP were resistant to polymyxin B, neomycin, or combination polymyxin B-neomycin. Only sulfamethoxazole possessed virtually no activity against either organism. Beta-lactamase production among strains of *H. influenzae* had no effect on antimicrobial susceptibility to the available topical antimicrobials.

DISCUSSION

H. influenzae or *S. pneumoniae* was recovered from nearly three-fourths of children with acute conjunctivitis. *H. influenzae* continues to be the most prevalent pathogen identified, also accounting for the majority of identified bacteria in patients with conjunctivitis-AOM syndrome. The rate of beta-lactamase-producing *H. influenzae* isolated from children with acute conjunctivitis has increased from 16% in the nasopharynx during the mid-1980s (10), compared with rates from conjunctivitis of 44% in the late 1980s (3), to our current rate of 69%. In contrast to previous reports (18), we recovered *H. influenzae* more frequently during the winter months. Although PNSP was isolated from only 8% of patients with conjunctivitis, it accounted for approximately one-third of recovered *S. pneumoniae* pathogens, a proportion similar to that of pathogens recovered from children with pneumococcal AOM in our community from 1992 to 1994 (2). The rate of PNSP among *S. pneumoniae* isolates in our study was threefold

TABLE 3. In vitro antimicrobial susceptibilities for *H. influenzae* isolates obtained from pediatric patients with acute conjunctivitis (1997–1998)

Antibiotics	MIC (μg/ml)[a]					
	Beta-lactamase-negative strains (n = 27)			Beta-lactamase-positive strains (n = 60)		
	50%	90%	Range	50%	90%	Range
Ampicillin	0.25	1	0.13–1	32	128	4–>128
Tobramycin	4	8	1–8	4	8	2–8
Gentamicin	4	8	2–16	4	8	4–32
Neomycin	16	16	8–64	16	16	8–64
Polymyxin B[b]	1	2	0.5–2	1	1	0.5–8
Polymyxin B-neomycin[b]	1.0/3.2	2.0/6.4	0.5/1.6–2/6.4	1.0/3.2	2.0/6.4	0.5/1.6–4/13
Trimethoprim	4	>32	0.13–>32	4	>32	0.25–>32
Polymyxin B-trimethoprim[b]	0.5/0.4	1.0/0.8	0.5/0.4–1/0.8	0.5/0.4	1.0/0.8	0.13/0.1–2/1.6
Ciprofloxacin	0.008	0.016	0.004–0.016	0.008	0.016	0.016–0.025
Ofloxacin	0.032	0.032	0.008–0.032	0.032	0.064	0.008–0.5
Chloramphenicol	1	2	0.5–16	0.5	1	0.5–16
Tetracycline	0.5	1	0.25–4	0.25	0.5	0.13–2
Erythromycin	8	16	0.25–16	8	16	4–16
Sulfamethoxazole	128	256	64–256	128	256	64–256
Clindamycin	16	64	4–64	16	32	4–64

[a] 50% and 90%, MIC_{50} and MIC_{90}, respectively.
[b] Polymyxin B is expressed in μg/ml. The specific activity of the formulation used was 7,500 IU/mg.

higher than that of the only other series (1994 to 1995) to report a rate of PNSP in conjunctival isolates (5).

Our susceptibility data shows diminished activity for gentamicin, tobramycin, polymyxin B-neomycin, polymyxin B-trimethoprim, and sulfamethoxazole against one or both of the most common causative pathogens of pediatric conjunctivitis. In fact, our sulfamethoxazole data would predict that the inexpensive sulfonamide class of antimicrobials currently in common use may have become no more effective than placebo. Topical sulfonamides should be used with caution until new clinical trials demonstrate their efficacy. In addition, sulfonamides and neomycin are commonly associated with hypersensitivity reactions, and sulfonamides are extremely irritating to the conjunctiva (13, 23). For *H. influenzae*, the two aminoglycosides tobramycin and gentamicin were more active than the neomycin combination but not as active as polymyxin-trimethoprim. Clinicians should suspect PNSP as the causative pathogen when children fail to respond to initial therapy with the combination topical antibiotics. The two topical fluoroquinolones possessed the highest intrinsic activity against all conjunctival pathogens, particularly for strains of PNSP. Both fluoroquinolones are approved by the Food and Drug Administration for the treatment of acute conjunctivitis in children older than 12 months. Tetracycline was notably active against most strains of bacteria, but concerns about dental staining in children younger than 8 years preclude its routine use in pediatric populations. In light of rapidly evolving resistant pathogens, in vitro susceptibility patterns may be the only practical means of evaluating the potential efficacy of the multitude of topical antimicrobials, of which most lack any current in vitro or in vivo clinical data. Most practitioners treat acute conjunctivitis in children with topical ophthalmological antimicrobials because (i) organisms are more rapidly eradicated with subsequent probable reduction in contagiousness and (ii) symptoms resolve quicker (13).

Neither breakpoints for susceptibility to topical antibiotics nor the appropriate formulation of combination antibiotics for in vitro testing have been determined. Thus, evaluating antibiotic pharmacokinetics-by comparing concentrations in tears with current MIC_{90}s—may better enable clinicians to predict efficacy for some topical antibiotics, similar to our assumptions about antibiotics for other illnesses, such as bacteremia and AOM. Despite the high concentration that topical antibiotics initially deliver to the conjunctiva, with continuous normal blinking and lacrimation, concentrations in adult tears fall below reported tobramycin, gentamicin, and ofloxacin MIC_{90}s for *H. influenzae* after 10, 120, and 240 min, respectively (15, 16). In contrast, after 240 min, ciprofloxacin tear concentrations (16.0 μg/ml) remain well above the MIC_{90} values for *H. influenzae* and *S. pneumoniae* (12). Yet, these kinetics may markedly overestimate the concentrations in tears of younger children who cry frequently when ill or upset or during the instillation of topical agents. Topical ointments probably deliver more-sustained concentrations of antibiotic to the conjunctiva, a fact that is possibly important in light of our tetracycline data. Unfortunately, in children older than 9 months, ointments are poorly tolerated because they blur the vision, and applying a layer of ointment with a metal-tipped tube to an ordinarily uncooperative, squirming youngster can be hazardous and is difficult for most parents. Alternatively, preliminary data suggests that a short course of beta-lactam oral antimicrobials may possibly eradicate the conjunctival infection (18).

Our data may have two important implications for the management of AOM. First, they confirm previous reports (3, 4) that when practitioners encounter children with conjunctivitis-AOM syndrome, they should more than ever select oral antimicrobials that possess good in vitro coverage for beta-lactamase-producing *H. influenzae*. Strains of *H. influenzae* recovered from acute conjunctivitis have been shown to be identical to those in AOM (4). Second, our susceptibility data for sulfamethoxazole further bolster recommendations (17) to avoid antibiotic chemoprophylaxis, particularly with sulfonamide drugs, for recurrent AOM. Our MIC_{50} and MIC_{90} (32 to >256 μg/ml) for sulfamethoxazole clearly showed that the two predominant pathogens of conjunctivitis, and subsequently AOM, are currently markedly resistant to the sulfonamides, all of which possess the same mechanism of action.

An aerobic bacterial pathogen was recovered in over half of newborns from 2 weeks to 2 months of age, a rate similar to that reported by Krohn and et al. (11). We did not test for *Chlamydia trachomatis*, a pathogen not prevented by the usual topical antimicrobials for neonatal prophylaxis (8). However, in the United States, *C. trachomatis* primarily causes conjunctivitis in children younger than 2 to 2 1/2 weeks (9, 19). Furthermore, in a multicenter study of children younger than 2 months old in the United States (11), *C. trachomatis* infection accounted for merely 2% of overall conjunctivitis, whereas infection with aerobic bacteria accounted for 44% of cases, the latter finding supported by our data. Thus, it would appear that initial empiric therapy for infants older than 2 weeks in lower-risk populations should probably target common aerobic pathogens (19). If no improvement is observed posttherapy or if conjunctivitis recurs within a week in children younger than 2 months, clinicians should consider culturing for aerobic pathogens, testing for *C. trachomatis*, and possibly empirically prescribing both topical and oral erythromycin.

Our study design had the following shortcomings. (i) The lack of formal selection criteria or randomization could have biased the seasonal pattern, rates of conjunctivitis-otitis syndrome, and epidemiologic and age differences. However, we doubt that this had much effect on the overall microbiology observed (no clinical correlates distinguish between *H. influenzae* and *S. pneumoniae* conjunctivitis), the rate of *H. influenzae* recovered in patients with conjunctivitis-otitis, or the respective bacterial susceptibility patterns. Conjunctivitis also has distinct age and seasonal patterns similar to those of AOM. Patients with AOM are likewise cultured based on the severity of illness and at the physician's discretion as a convenience sample. In addition, our rate of conjunctivitis-otitis syndrome is similar to data from our previous clinical trial (10) and the work of others. (21) (ii) *M. catarrhalis* was excluded as a pathogen because of the lack of a reliable screen on the initial agar plates, its low reported incidence (1 to 6%) (3), and its high propensity to spontaneously resolve. However, we did not observe any *S. pyogenes*, unlike during our earlier work (10). (iii) The correlation between in vitro resistance and efficacy is unknown, particularly in a self-limited disease such as conjunctivitis, but duration of symptoms and potential for infectivity is reduced with more-active antibiotics.

Our data show that the bacterial pathogens *H. influenzae* and *S. pneumoniae* continue to be the major pathogens recovered from children who were diagnosed with acute conjunctivitis in the 1990s (7). *S. pneumoniae* organisms resistant to high levels of penicillin are now present in one-fourth of the cases of pneumococcal conjunctivitis and over two-thirds of isolated *H. influenzae* strains produce beta-lactamase. When clinicians select initial antibiotic therapy for children with acute conjunctivitis, topical antibiotics such as the polymyxin combinations or other antibiotics more active against *H. influenzae* would be reasonable. Sulfonamides are probably no longer an appropriate choice. Earlier in vivo comparative clinical trials for pediatric conjunctivitis have shown that gentamicin or sodium sul-

facetamide was not as effective as polymyxin-trimethoprim against *H. influenzae* (13). In contrast, tobramycin was as effective as the more-active ciprofloxacin, but PNSP was not reported (7). If first-line topical therapy for acute conjunctivitis in children older than 2 months fails, clinicians should then consider obtaining a standard aerobic culture of the conjunctiva and initiating therapy with a topical fluoroquinolone (off-label usage between 2 and 12 months of age) to cover for both PNSP and *H. influenzae*. Beta-lactamase stable oral antibiotics against *H. influenzae*, such as third-generation cephalosporins or amoxicillin-clavulanate, should be added for the treatment of conjunctivitis-otitis syndrome (1).

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